APPENDIX 3.9.4.

RISK ANALYSIS FOR ANTIMICROBIAL RESISTANCE

Article 3.9.4.1.

Guidelines for analysing the risks to animal and public health from antimicrobial resistant bacteria of animal origin

1) Introduction

The incorrect use of antimicrobials for therapy, prophylaxis and growth promotion in animals can reduce their efficacy in animal and human medicine, through the development of antimicrobial resistant strains of pathogenic bacteria. This risk may be represented by the loss of therapeutic efficacy of one or several antimicrobial drugs and includes the emergence of multi-resistant bacteria.

2) Objective

The principal aim of risk analysis for antimicrobial resistance in bacteria from animals is to provide Member Countries with a transparent, objective and defensible method of assessing and managing the human and animal health risks associated with the development of resistance arising from the use of antimicrobials in animals.

3) The risk analysis process

A generic risk analysis process is described in Section 1.3. of the *Terrestrial Code*.

A qualitative risk assessment should always be undertaken. Its outcome will determine whether progression to a quantitative risk assessment is feasible and/or necessary.

4) Hazard identification

For the purposes of this appendix, the hazard is the resistance determinant that emerges as a result of the use of a specific antimicrobial in animals. This definition reflects the development of resistance in a species of pathogenic bacteria, as well as the development of a resistance determinant that may be passed from one species of bacteria to another. The conditions under which the hazard might produce adverse consequences include any feasible scenarios through which humans or animals could become exposed to a pathogen which contains that resistance determinant, fall ill and then be treated with an antimicrobial that is no longer effective because of the resistance.

5) Risk assessment

The assessment of the risk to human and animal health from antimicrobial-resistant bacteria resulting from the use of antimicrobials in food-producing animals should examine:

a) the likelihood of emergence of resistant bacteria arising from the use of antimicrobial(s), or more particularly, production of the resistant determinants if transmission is possible between bacteria;

b) consideration of all pathways and their importance, by which humans could be exposed to

these resistant bacteria or resistance determinants, together with the possible range of bacterial load ingested at the moment of exposure;

c) the consequences of exposure and the estimated probability of its occurrence.

Article 3.9.4.2.

Analysis of risks to human health

1) Definition of the risk

The infection of humans with bacteria that have acquired resistance to a specific antimicrobial used in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the human infection.

2) Hazard identification

– Bacteria that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial(s) in animals

– Bacteria having obtained a resistance determinant(s) from another bacteria which have acquired resistance arising from the use of an antimicrobial(s) in animals.

The identification of the hazard must include consideration of the class or subclass of the antimicrobial(s).

3) Release assessment

A release assessment describes the biological pathways necessary for the use of a specific antimicrobial in animals to lead to the release of resistant bacteria or resistance determinants into a particular environment, and estimating either qualitatively or quantitatively the probability of that complete process occurring. The release assessment describes the probability of the release of each of the potential hazards under each specified set of conditions with respect to amounts and timing, and how these might change as a result of various actions, events or measures.

The following factors should be considered in the release assessment:

– species of animal treated with the antimicrobial(s) in question

– number of animals treated, geographical distribution of those animals

– variation in methods of administration of the antimicrobial(s)

– bacteria developing resistance as a result of the antimicrobial(s) use

– mechanism of direct or indirect transfer of resistance

– cross-resistance and/or co-resistance with other antimicrobials

– surveillance of animals, animal products and waste products for the existence of resistant bacteria.

4) Exposure assessment

An exposure assessment describes the biological pathways necessary for exposure of humans to the resistant bacteria or resistance determinants released from a given antimicrobial use in animals, and estimating the probability of the exposures occurring. The probability of exposure to the identified hazards is estimated for specified exposure conditions with respect to amounts, timing, frequency, duration of exposure, routes of exposure and the number, species and other characteristics of the human populations exposed.

The following factors should be considered in the exposure assessment:

- human demographics and food consumption patterns, including traditions and cultural practices
- prevalence of food and/or the animal environment contaminated with resistant bacteria
- prevalence of animal feed contaminated with resistant bacteria
- cycling of resistant bacteria between humans, animals and the environment
- steps of microbial decontamination of food
- microbial load in contaminated food at the point of consumption
- survival capacity and redistribution of resistant bacteria during the food production process (including slaughtering, processing, storage, transportation and retailing)
- disposal practices for waste products and the opportunity for human exposure to resistant bacteria or resistance determinants in those waste products
- point of consumption of food (professional catering, home cooking)
- variation in consumption and food-handling methods of exposed populations and subgroups of the population
- capacity of resistant bacteria to become established in human intestinal flora
- human-to-human transmission of the bacteria under consideration
- capacity of resistant bacteria to transfer resistance to human commensal bacteria
- amount and type of antimicrobials used in response to human illness
- dose, route of administration (oral, parenteral) and duration of human treatment
- pharmacokinetics (metabolism, bioavailability, access to intestinal flora).

5) Consequence assessment

A consequence assessment describes the relationship between specified exposures to resistant bacteria or resistance determinants and the consequences of those exposures. A causal process must exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of them occurring.

The following factors should be considered in the consequence assessment:

– dose-response relationships

– variation in susceptibility of exposed populations or subgroups of the population

– variation and frequency of human health effects resulting from loss of efficacy of antimicrobials

– changes in human medicinal practices resulting from reduced confidence in antimicrobials

– changes in food consumption patterns due to loss of confidence in the safety of food products and any associated secondary risks

– associated costs

– interference with a classical first line of antimicrobial therapy in humans

– perceived future usefulness of the drug (time reference).

6) Risk estimation

A risk estimation integrates the results from the release assessment, exposure assessment and consequence assessment to produce overall estimates of risks associated with the hazards. Thus, risk estimation takes into account the whole of the risk pathway from hazard identification to the unwanted consequences.

The following factors should be considered in the risk estimation:

– number of people falling ill

– increased severity or duration of disease

– number of person/days of illness per year

– deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)

– importance of the pathology caused by the bacteria

– absence of alternate antimicrobial therapy

– incidence of resistance observed in humans

– some arbitrary scale of consequences to allow weighted summation of different risk impacts (e.g. illness and hospitalisation).

7) Risk management options

Risk management options have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.

Article 3.9.4.3.

Analysis of risks to animal health

1) Definition of the risk

The infection of animals with bacteria that have acquired resistance from the use of a specific antimicrobial(s) in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal infection.

2) Hazard identification

– Bacteria that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial(s) in animals

– Bacteria having obtained a resistance determinant(s) from another bacteria which have acquired resistance arising from the use of an antimicrobial(s) in animals.

The identification of the hazard must include considerations of the class or subclass of the antimicrobial(s).

3) Release assessment

The following factors should be considered in the release assessment:

– animal species treated

– number of animals treated and their geographical distribution

– site and type of infection

– variation in routes of administration

– development of resistant bacteria

– mechanisms and pathways of resistance transfer

– cross-resistance and/or co-resistance

– surveillance of animals, animal products and waste products for resistant bacteria.

4) Exposure assessment

The following factors should be considered in the exposure assessment:

– prevalence and trends of resistant bacteria in clinically ill and clinically unaffected animals

– prevalence of resistant bacteria in feed /the animal environment

– animal-to-animal transmission of the resistant bacteria

– number/percentage of animals treated

– dissemination of resistant bacteria from animals (animal husbandry methods, movement of animals)

– quantity of antimicrobial(s) used in animals

– treatment regimens (dose, route of administration, duration)

– survival capacity of resistant bacteria

– exposure of wild life to resistant bacteria

– disposal practices for waste products and the opportunity for human exposure to resistant bacteria or resistance determinants in those products

– capacity of resistant bacteria to become established in animal intestinal flora

– exposure to resistance determinants from other sources

– dose, route of administration and duration of treatment

– pharmacokinetics (metabolism, bioavailability, access to intestinal flora)

– cycling of resistant bacteria between humans, animals and the environment.

5) Consequence assessment

The following factors should be considered in the consequence assessment:

– dose-response relationships

– variation in susceptibility of exposed populations and subgroups of the populations

– variation and frequency of animal health effects resulting from loss of efficacy of antimicrobials

– changes in veterinary medicine practices resulting from reduced confidence in antimicrobials

– associated cost

– perceived future usefulness of the drug (time reference).

6) Risk estimation

The following factors should be considered in the risk estimation:

– number of therapeutic failures due to resistant bacteria

– animal welfare

– economic cost

– deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)

– incidence of resistance observed in animals.

7) Risk management options

The recommendations in this *Terrestrial Code* apply.